ELECTROTRANSPORT AGENT DELIVERY METHOD AND APPARATUS

TECHNICAL FIELD

The present invention generally concerns a method and apparatus for the electrically assisted delivery of a therapeutic agent (e.g., a drug) through a body surface (e.g., intact skin) at increased efficiency. This invention is particularly applicable to the electrotransport of highly potent therapeutic agents which are to be delivered at small dosage levels.

BACKGROUND OF THE INVENTION

The present invention concerns in vivo methods and apparatuses for transdermal electrotransport delivery of therapeutic agents, typically drugs. Herein the terms "electrotransport", "iontophoresis" and "iontophoretic" are used to refer to methods and apparatus for transdermal delivery of therapeutic agents, whether charged or uncharged, by means of an applied electromotive force to an agent-containing reservoir. The particular therapeutic agent to be delivered may be completely charged (i.e., 100% ionized), completely uncharged, or partly charged and partly neutral. The therapeutic agent or species may be delivered by electromigration, electroosmosis or a combination of these processes. Electroosmosis has also been referred to as electrohydrokinesis, electro-convection, and electrically-induced osmosis. In general, electroosmosis of a therapeutic species into a tissue results from the migration of solvent, in which the species is contained, as a result of the application of electromotive force to a reservoir containing the therapeutic species.

As used herein, the terms "electrotransport", "iontophoresis" and "iontophoretic" refer to (1) the delivery of charged drugs or agents by electromigration, (2) the delivery of uncharged drugs or agents by the process of electroosmosis, (3) the delivery of species by transport processes which include an electroporation step (See, e.g., Weaver et al. U.S. Patent 5,019,034), (4) the delivery of charged drugs or agents by the combined processes of electromigration and electroosmosis, and/or (5) the delivery of

1   a mixture of charged and uncharged drugs or agents by the combined

2   processes of electromigration and electroosmosis, combinations of the above

3   processes to deliver either or both of charged or uncharged species.

4   Iontophoretic devices for delivering ionized drugs through the skin

5   have been known since the early 1900's. See for example, Deutsch U.S.

6   Patent 410,009. In presently known electrotransport devices, at least two

7   electrodes or electrode assemblies are used. Both electrodes/electrode

8   assemblies are disposed so as to be in intimate electrical contact with some

9   portion of the skin of the body. One electrode, called the active or donor

10   electrode, is the electrode from which the ionic substance, agent,

11   medicament, drug precursor or drug is delivered into the body through the

12   skin by iontophoresis. The other electrode, called the counter or return

13   electrode, serves to close the electrical circuit through the body. In

14   conjunction with the patient's skin contacted by the electrodes, the circuit is

15   completed by connection of the electrodes to a source of electrical energy,

16   e.g., a battery. For example, if the ionic substance to be delivered into the

17   body is positively charged, then the positive electrode (the anode) will be the

18   active electrode and the negative electrode (the cathode) will serve to

19   complete the circuit. If the ionic substance to be delivered is negatively

20   charged, then the cathodic electrode will be the active electrode and the

21   anodic electrode will be the counter electrode.

22   As is discussed above, electrotransport delivery devices can be used

23   to deliver uncharged drugs or agents into the body, e.g, transdermally. This

24   is accomplished by a process called electroosmosis. Electroosmosis is the

25   (e.g., transdermal) flux of a liquid solvent (e.g., the liquid solvent containing

26   the uncharged drug or agent) which is induced by the presence of an electric

27   field imposed across the skin by the donor electrode.

28   Electrotransport electrode assemblies/devices generally include a

29   reservoir or source of the beneficial agent or drug (preferably an ionized or

30   ionizable species or a precursor of such species), which is to be delivered

31   into the body by electrotransport. Examples of such reservoirs or sources

1   include a pouch as described in Jacobsen U.S. Patent 4,250,878, a pre-

2   formed gel body as disclosed in Webster U.S. Patent 4,382,529 and Ariura,

3   et al. U.S. Patent 4,474,570 and a receptacle containing a liquid solution as

4   disclosed in Sanderson, et al. U.S. Patent 4,722,726. Such drug reservoirs

5   are connected to the anode or the cathode of an electrotransport device to

6   provide a fixed or renewable source of one or more desired species or

7   agents. Electrical current is typically applied to the reservoir by means of a

8   current distributing member, which may take the form of a metal plate, a foil

9   layer, a conductive screen, or a polymer film loaded with an electrically

10   conductive filler such as silver or carbon particles. The current distributing

11   member, including any appropriate connectors and associated connective

12   conductors such as leads, and the reservoir comprise an electrode assembly

13   herein.

14   The prior art has recognized that "competitive" ionic species having

15   the same charge (i.e., the same sign) as the drug ions being delivered by

16   electrotransport have a negative impact on electrotransport drug delivery

17   efficiency. The efficiency (E) of electrotransport delivery of a particular

18   species is defined herein as the rate of electrotransport delivery of that

19   species per unit of applied electrotransport current (mg/mA-h). The prior art

20   further recognized that competitive ionic species were inherently produced

21   during operation of these devices. The competitive species produced are

22   dependent upon the type of electrode material which is in contact with the

23   drug solution. For example, if the electrode is composed of an

24   electrochemically inert material (e.g., platinum or stainless steel), the

25   electrochemical charge transfer reaction occurring at the electrode surface

26   tended to be water electrolysis since water is the overwhelmingly preferred

27   liquid solvent used in electrotransport drug solutions. Water electroysis

28   produces competing hydronium ions at the anode (in the case of cationic

29   electrotransport drug delivery) and competing hydroxyl ions at the cathode

30   (in the case of anionic electrotransport drug delivery). On the other hand, if

31   the electrode is composed of an electrochemically oxidizable or reducible

4

species, then the electrode itself is oxidized or reduced to form a competitive
ionic species. For example, Untereker et al U.S. Patent 5,135,477 and
Petelenz et al U.S. Patent 4,752,285 recognize that competitive ionic species
are electrochemically generated at both the anode and cathode of an
electrotransport delivery device. In the case of an electrotransport delivery
device having a silver anodic donor electrode, application of current through
the silver anode causes the silver to become oxidized ($Ag \rightarrow Ag^+ + e^-$)
thereby forming silver cations which compete with the cationic drug for
delivery into the skin by electrotransport. The Untereker and Petelenz
patents teach that providing a cationic drug in the form of a halide salt
causes a chemical reaction which removes the "competing" silver ions from
the donor solution (i.e., by reacting the silver ions with the halide counter ion
of the drug to form a water insoluble silver halide precipitate; $Ag^+ + X^- \rightarrow$
AgX), thereby achieving higher drug delivery efficiency. In addition to these
patents, Phipps et al PCT/US95/04497 filed on April 7, 1995 teaches the use
of supplementary chloride ion sources in the form of high molecular weight
chloride resins in the donor reservoir of a transdermal electrotransport
delivery device. These resins are highly effective at providing sufficient
chloride for preventing silver ion migration, yet because of the high molecular
weight of the resin cation, the resin cation is effectively immobile and hence
cannot compete with the drug cation for delivery into the body.

The prior art has long recognized that the application of electric
current through skin causes the electrical resistance of the skin to decrease.
See, for example, Haak et al U.S. Patent 5,374,242 (Figure 3). Thus, as the
electrical resistance of the skin drops, lower voltages are needed to drive a
particular level of electrotransport current through the skin. This same
phenomenon is observed in a technique referred to as "electroporation" of
the skin. See Weaver et al U.S. Patent 5,019,034. Electroporation involves
the application of short, high voltage electrical pulses to produce what is
characterized as a transient (e.g., decreasing to normal levels in 10 to 120
sec. for excised frog skin) increase in tissue permeability. Electroporation is

1   also characterized by the creation of pores in lipid membranes due to

2   reversible electrical breakdown. Electroporation does not, itself, deliver any

3   drug but merely prepares the tissue thereby treated for delivery of drug by

4   any of a number of techniques, one of which is iontophoresis.

5

6   **DISCLOSURE OF THE INVENTION**

7   The present invention arises from the discovery that, under specified

8   conditions of applied electrotransport current density (generally expressed in

9   units of microamperes/cm^2 herein) and application time, the electrotransport

10 transdermal drug delivery efficiency is enhanced. Electrotransport drug

11 delivery efficiency, E, is defined as the rate of transdermal electrotransport

12 delivery (mg/h) per unit of applied electrotransport current (mA), and

13 expressed in units of milligrams of agent (e.g., drug) delivered per milliamp-

14 hour of applied electric current (mg/mAh). Electrotransport delivery

15 efficiency, in some aspects of its meaning, is analogous to transport number.

16 Transport number is a unitless quantity, less than one, indicating the

17 fractional charge carried by a particular ionic species, e.g., a drug or agent,

18 during electrotransport delivery. Electrotransport delivery efficiency, as

19 defined herein, is more broadly applicable to include the transport of

20 uncharged species and is more reflective of the scope of the invention.

21   The enhancement of the skin's electrotransport efficiency has been

22 found to be non-transitory, i.e., to last for at least several minutes to several

23 hours or longer after application of this invention. This invention induces

24 (e.g., through a pre-treatment or pre-application step in which species are

25 delivered) a high efficiency drug-transmissive state in the skin to which it is

26 applied. The induced, high efficiency state continues and can be utilized to

27 deliver drug or other therapeutic agent transdermally via electrotransport with

28 increased efficiency. In usual circumstances, this will permit delivery of drug

29 with more precise control and at a lower current. This phenomenon has only

30 been found in the transdermal delivery of drug or agent through intact living

6

1 skin or tissue, (i.e., in vivo) and is not exhibited in dead skin (i.e., excised

2 skin through which species are electrotransported in vitro).

3   Generally speaking, this invention involves delivery of a charged

4 species at or above a pre-determined threshold current density I_c for at least

5 a predetermined period of time t_c (e.g., for a predetermined pulse width)

6 through the site of drug delivery, e.g., intact skin. In this manner, the treated

7 skin exhibits a statistically significant, non-transitory increase in drug delivery

8 efficiency relative to skin which has not been so treated. Generally

9 speaking, utilization of this invention will significantly increase the drug/agent

10 delivery efficiency and reduce or eliminate efficiency variability of the skin

11 segment which is so treated. Since electrotransport delivery efficiency

12 remains elevated or less variable after utilization of this invention (relative to

13 untreated skin), utilization of this invention permits the delivery of drug or

14 agent through intact skin by electrotransport with increased control and

15 efficiency.

16   Briefly, in one aspect, the present invention is a method of

17 electrotransport drug or agent delivery through a body surface involving the

18 steps of:

19   delivering ionic species by electrotransport at a sufficient

20   current density and over a sufficient period which will change or

21   convert the transport efficiency of the body surface through which the

22   ionic species is delivered to a non-transitory state of higher species

23   delivery efficiency; and thereafter

24   delivering drug or agent through the body surface while in its

25   high efficiency state.

26

27   In a preferred practice, current density and species delivery time are

28 selected to maintain the higher efficiency species delivery state of the body

29 surface. This invention also includes the preferred practice of intentionally

30 renewing the highly efficient species delivery state so as to optimize drug

31 delivery efficiency if drug or agent delivery conditions are used which do not

1   periodically renew it. In another preferred practice, the present invention is

2   utilized to deliver drug or agent transdermally, i.e., through intact skin. In yet

3   a further preferred practice, the present invention is used to deliver drug or

4   agent through intact, live, human skin.

5   In the practice of this invention, the precise current density and

6   treatment time period needed to convert untreated skin to a highly

7   transmissive state have been found to be fairly specific to the drug or

8   therapeutic agent to be delivered. However, for the electrotransport delivery

9   of analgesics, which have been the primary focus of this invention, a

10   treatment of the body site through which drug is to be delivered for a time

11   period of at least 5 msec, and preferably at least 10 msec, at a current

12   density of at least about 40 $\mu A/cm^2$, preferably at least about 50 $\mu A/cm^2$ and

13   most preferably at least about 70 $\mu A/cm^2$ appears to convert the body site so

14   treated to a highly drug transmissive state as defined in this invention. This

15   invention arises because of the discovery that electrotransport delivery

16   efficiency is highly dependent (i.e., it is non-constant) at current densities in

17   the range of about 0 to about 30 $\mu A/cm^2$, is moderately dependent upon

18   current density in the range of about 40 to about 70 $\mu A/cm^2$ and is relatively

19   independent of current density at current densities in excess of about 70

20   $\mu A/cm^2$. This unexpected change in efficiency (in theory, efficiency is not

21   predicted to change with increasing current density) permits transdermal

22   electrotransport delivery of drug with significantly enhanced efficiency.

23   A second unexpected result is achieved in the practice of the present

24   invention, i.e., the change of the skin to the higher efficiency transmissive

25   state is non-transitory with the skin remaining in the higher, and more stable,

26   efficiency state for minutes to hours after the initial transformation, even in

27   cases where the subsequently applied electrotransport current density is

28   lowered to a level below I_c or turned off, completely. In other words, when

29   the skin site has been converted to a highly efficient agent transmissive state

30   by applying a pulsing electric current, the current pulses having a sufficient

31   magnitude to provide a current density at or above the critical current density

I_c, and preferably over pulse widths of at least 5 msec reduction in applied electrotransport current (and therefore current density) does not cause the skin to immediately return to its initial, lower efficiency state. This observation respecting in vivo drug delivery is critically important to electrotransport system design.

The term "non-transitory" as used herein, when referring to the high efficiency electrotransport agent delivery state, means of sufficient length to permit drug to be delivered to achieve a therapeutic effect. Thus, for example, a relatively inexpensive ionic species may be used to trigger conversion of, e.g., a skin site, to a highly efficient and more stable ionic species delivery state, and thereafter relatively more expensive drug or agent may be delivered at greater efficiency and stability by electrotransport. Where the drug or agent is inexpensive, it may be used to convert the body delivery site to the highly efficient and more stable state, and thereafter may be delivered with greater efficiency, i.e., at lower current density and at greater stability.

The term "high/higher efficiency state" as used herein means conversion of any particular body or skin site to a state in which drug or agent delivery is at least 10% (preferably 20%) more efficient than the same skin site prior to conversion in accordance with this invention. Generally, the parameter which will be most reflective of this efficiency increase is the electrotransport delivery efficiency measured in milligrams of drug delivered per milliamp-hour of applied electrotransport current.

The term "more stable efficiency" as used herein means conversion of a body surface site from a state of more variable electrotransport agent delivery efficiency to one of less variability by exposure of the body site to a current density above the critical current density I_c for a time period longer than the critical time, t_c. Critical current density for purposes of increased stability, has been found to be as low as about 40 $\mu A/cm^2$.

In a preferred practice of this invention, it is desirable to be able to change, precisely, drug dosage after the body site has been converted to a

1   highly efficient drug or agent delivery state. In accordance with this

2   invention, total drug or agent delivered (i.e., dosage) may be adjusted while

3   maintaining the required current density to retain the most efficient and

4   stable state, i.e., independent of average current applied by the alternatives

5   of: (a) in a pulsed output electrotransport system, adjustment of device duty

6   cycle while maintaining average current density above the critical current

7   density; (b) in an electrotransport device employing a pulsed output,

8   maintaining constant peak current and pulse width while adjusting pulse

9   frequency to adjust total drug or agent delivered, or (c) the intentional

10 inclusion in and delivery from an "in line" (i.e., to deliver drug) component

11 or subassembly of an electrotransport device of competitive co-ions not

12 having a therapeutic effect converts the system to a stable drug flux at a

13 current density above the critical current density. Delivery of competitive co-

14 ions, for a given current, in addition to the drug or agent ions, provides

15 adequate current density but permits controlled modification of the quantity of

16 therapeutic agent delivered. Delivery of competitive co-ions from, e.g., the

17 drug reservoir, also reduces potentially expensive and potent total drug or

18 agent delivered.

19   Another way to use an inexpensive ionic species to trigger the skin

20 conversion is to utilize a reverse polarity system. One example of such a

21 system would first drive the anionic drug counter ion from the donor reservoir

22 and the cationic substance from the counter reservoir for the time required to

23 convert the skin to a high efficiency state and then reverses polarity, thereby

24 moving the drug cation into the skin.

25   In one practice of this invention, the highly potent analgesic drug,

26 fentanyl, is transdermally delivered via electrotransport at very low current

27 density under conditions at which fentanyl delivery tends to be unstable, i.e.,

28 to exhibit unacceptable drug delivery efficiency variability. Addition of a

29 chloride salt, e.g., sodium chloride, to the electrode assembly drug reservoir

30 provides sufficient co-deliverable, competitive ion (i.e. Na^+) to stabilize

31 fentanyl delivery. In this manner, fentanyl efficiency variability also is

1 reduced or eliminated. These and other aspects of this invention will be

2 discussed below.

3

4 ## BRIEF DESCRIPTION OF THE DRAWINGS

5 A better understanding of the present invention, as well as other

6 objects and advantages thereof, will become apparent upon consideration of

7 the following modes for carrying out the invention especially when taken with

8 the accompanying drawings, wherein:

9 FIG. 1 is a graph of transdermal electrotransport drug delivery

10 efficiency (E) versus applied electrotransport current density (I_d) for _in vivo_

11 delivery of fentanyl;

12 FIG. 2 is a graph of electrotransport current versus time, showing

13 three pulsed current waveforms having differing duty cycles;

14 FIG. 3 is an exploded perspective view of a transdermal

15 electrotransport drug delivery device which can be used in accordance with

16 the method of the present invention.

17 FIG. 4 is a graph of electrotransport current versus time, showing two

18 pulsed current waveforms having the same peak current and pulse width but

19 different pulsing frequencies;

20 FIG. 5 is a graph of mean serum fentanyl concentration versus time,

21 showing how initial electrotransport administered doses increase subsequent

22 fentanyl delivery through a 24 hour period;

23 FIG. 6 is a graph of average serum fentanyl concentration, as a

24 function of time, for applied electrotransport current densities of 10, 20 and

25 40 $\mu A/cm^2$;

26 FIG. 7 is a graph of serum fentanyl concentration versus time for

27 delivery of fentanyl at pulsing frequencies of 1, 10, and 625 Hz; and

28 FIG. 8 is a graph of serum goserelin concentration versus time, for

29 applied electrotransport current densities of 50 and 100 $\mu A/cm^2$.

30

31

MODES FOR CARRYING OUT THE INVENTION

The present invention is based upon the discovery that the efficiency
(E) of transdermal electrotransport agent (e.g., drug) delivery is, at least at
lower applied electrotransport current densities, dependent on the applied
electrotransport current density (I_d). This phenomenon is illustrated
graphically in FIG. 1. Specifically, we have discovered that when
electrotransport current densities at or above a critical current density level,
I_c, are applied to the skin of living animals for a sufficient period of time, at
least as long as a critical period of time t_c on the order of several
milliseconds, the electrotransport drug delivery efficiency (E) increases and
becomes independent of the level of applied electrotransport current density.
It is important to note that the variable electrotransport delivery efficiency
effect is a limited exception to the widely reported principle that transdermal
electrotransport drug flux is dependent (i.e., linearly dependent) upon the
level of applied electrotransport current. Our discovery is that this principle is
only true at current densities at or above a critical current density level I_c.
Thus, we have discovered that, at applied current densities below the critical
current density level I_c, the rate of electrotransport drug delivery per unit of
applied electrotransport current is not constant as has been previously
assumed. Not only is the electrotransport drug delivery efficiency (E)
variable at lower current densities, it is also lower than at current densities
above the critical level I_c. Thus, at applied current densities below I_c, the
electrotransport delivery is less efficient in that more electrotransport current
must be applied to deliver a predetermined amount of drug. A still further
aspect of our discovery is that the interpatient variability in transdermal
electrotransport efficiency is lower at applied current densities above the
critical level I_c and higher at applied current density levels below the critical
level I_c.

In general, the critical current density level I_c for human skin is in the
range of about 40 to 100 $\mu A/cm^2$, although the critical level I_c will vary
somewhat depending upon (i) the particular drug being delivered, (ii) the

1   particular patient being treated, and (iii) the particular skin location of the

2   patient wearing the electrotransport device. Typically, a current density at or

3   above the critical level I_c need only be applied for several milliseconds to

4   several seconds before the skin enters the high efficiency drug transfer state.

5   However, applied current densities below the critical level I_c are unable to

6   transform the skin into the high efficiency transfer state, even when these

7   low level current densities are applied for extended periods of time (e.g., up

8   to several hours application). This transformation of the skin to a higher

9   efficiency delivery state occurs only in living animals and does not occur with

10   excised skin taken from living or dead animals, i.e., the skin transformation

11   has not been found to occur when in vitro flux studies were run.

12   Once the skin has been transformed into the high efficiency transfer

13   state, it tends to remain in that state for an extended period of time (e.g., up

14   to 24 hours) even if no further electrotransport current is thereafter applied to

15   the skin or if only low level current densities (i.e., current densities less than

16   the critical level I_c) are thereafter applied to the skin. This result is illustrated

17   in FIG. 5 and is discussed below. The "transformed" skin is in general only

18   those skin sites which are in contact with the donor and counter

19   electrodes/reservoirs of the electrotransport delivery device and through

20   which skin sites the applied current has been passed. Thus, if a skin site on

21   the upper arm of a patient has been transformed by application of

22   electrotransport current densities at or above the critical level I_c , the skin on

23   the lower (same) arm, the legs, torso or other arm of the patient does not

24   become transformed. The skin transformation of this invention is a localized

25   phenomenon which is limited to those portions of the skin to which the donor

26   and counter electrodes/reservoirs are attached. Since the skin at the

27   counter electrode site also is converted to the higher efficiency delivery state,

28   methods and devices for delivering agents from the "donor" and "counter"

29   electrodes or both electrodes (e.g., by alternating current polarity) are within

30   the scope of this invention.

1   Our discovery is particularly critical in those transdermal

2 electrotransport drug delivery regimens wherein the drug is delivered at two

3 (or more) different dosing levels, one dosing level being administered at a

4 current density below the critical level I_c and another dosing level being

5 administered at a current density above the critical level. For example,

6 many drugs are adapted to be administered at a low dose baseline rate for

7 extended periods, the baseline rate being interrupted periodically by periods

8 of higher dosing. Examples of drugs which are administered in this fashion

9 include (1) analgesics, such as fentanyl and sufentanil, which are

10 administered at a low baseline level to treat (e.g., chronic) pain and which

11 are periodically delivered at higher doses to treat more severe episodes of

12 pain; (2) anti-emetics, such as the 5HT3 receptor antagonists ondansetron

13 and granisetron, which are administered continuously at low levels (e.g.,

14 during weeks over which a patient is undergoing chemotherapy) and which

15 are periodically administered at higher dosing levels (i.e., during the actual

16 chemotherapeutic administration); (3) anti-epileptics, such as phenytoin,

17 which are delivered continuously at low baseline levels and periodically at

18 higher levels when the patient is undergoing an epileptic seizure; and (4)

19 anti-diabetic drugs, such as insulins, which can be delivered continuously at

20 low baseline levels and periodically (e.g., around meal times) at higher

21 levels. The problem encountered with this type of transdermal

22 electrotransport drug administration is that after the drug is administered at

23 the higher dosing rate (with the applied current density above the critical

24 level, I_c), when the applied electrotransport current is readjusted to apply the

25 original lower baseline level, the transdermal electrotransport drug flux does

26 not return to the same baseline level. The drug flux instead falls to a level

27 somewhere between the original baseline rate and the high dosing rate,

28 because the skin has been transformed into a higher efficiency drug delivery

29 state. For example, if the efficiency is enhanced by a factor of two, after

30 the skin has experienced a current density above the critical current density,

31 and then the current is lowered to the original baseline current, the drug

1   delivery rate would be twice that experienced before the transformation. The

2   higher baseline rate could result in a drug overdose if the electrotransport

3   system does not compensate for this shift in efficiency. To eliminate this

4   problem, the electrotransport system should reduce the current applied (e.g.,

5   by approximately a factor of two) after the skin has experienced a current

6   density greater than I_c. With reference to FIG. 1, data point 2 is a likely

7   efficiency that would be experienced at the drug delivery site were current

8   (and therefore current density) reduced after exposure of the body site to a

9   current density at or above I_c for at least a period of time t_c. At data point

10   "2", the electrotransport agent delivery efficiency is higher than the agent

11   delivery efficiency which was experienced initially (i.e., before exposure to a

12   current density above I_c) at the current density of 20 $\mu A/cm^2$.

13   A more elegant approach to this problem is to apply a pulsed

14   electrotransport current to the skin, the pulsing current having a magnitude

15   above the critical level I_c, and to modify the duty cycle of the pulses to

16   increase or decrease the amount of drug delivered. The term "duty cycle"

17   as used herein is the ratio of "on" time interval to the period of time of one

18   cycle (i.e., the ratio of the pulse-duration time to the pulse-period) and is

19   usually expressed as a percent. For example, if a device is "on" for 500 ms

20   of a 1 sec cycle, then the device is operating in a 50% duty cycle. In this

21   practice of the invention, the magnitude of the current pulses is selected in

22   view of the known area of the surface from which drug is delivered, thereby

23   defining a fixed and known current density (i.e., the ratio of current to the

24   area from which current flows). Thus, if it is decided, based upon application

25   of the above principles, that a specific maximum current for a given anode

26   surface area e.g., I_{max}, will provide the enhanced efficiency drug delivery

27   discussed above, then by increasing or decreasing the duty cycle, the

28   amount of drug delivered at the high efficiency state can be increased or

29   decreased without causing the applied current density to change. In

30   choosing the parameters of drug delivery if using this approach, the

31   magnitude of the current pulses is selected so that the resulting current

1 density transforms the skin into the high efficiency state and the duty cycle

2 of the current pulses is altered to adjust the drug delivery rate (i.e., a low

3 dose of drug is administered by a high density (i.e., greater than or equal to

4 I_c) pulsing current having a low duty cycle and a high dose of drug is

5 administered by the same magnitude current density but being pulsed at a

6 longer pulse width corresponding to a higher duty cycle.

7 This aspect of the invention is more specifically illustrated in Fig. 2

8 where waveforms for three different pulsing electrotransport currents of the

9 same frequency are shown. In FIG. 2 time is illustrated on the horizontal

10 axis, while current amplitude is illustrated on the vertical axis. The three

11 current waveforms shown in FIG. 2 all have the same magnitude, and hence

12 the same maximum applied current density I_{max} for an electrotransport

13 delivery device of any one size. This particular current density I_{max} is greater

14 than the critical current density level I_c. The three current waveforms have

15 differing duty cycles, which is the percentage of time during which the

16 current is applied. The three waveforms have duty cycles of 75% (top

17 waveform), 50% (middle waveform) and 25% (bottom waveform). Thus, the

18 25% duty cycle waveform delivers drug transdermally by electrotransport at

19 about one-half the dosing level of the 50% duty cycle waveform and about

20 one-third the dosing level of the 75% duty cycle waveform. All three

21 waveforms administer drug transdermally by electrotransport through skin

22 which is transformed into the high efficiency transfer state by reason of I_{max}

23 being greater than I_c.

24 In a further practice of this invention, the pulsing frequency of a

25 pulsed current waveform is adjusted to control the overall quantity of drug

26 delivered while holding the pulse width constant and maintaining the

27 magnitude of current pulses at or above I_c. In this manner, current density is

28 maintained at or above the level which transforms the skin into the high

29 efficiency state. Exemplary of this, a device employing a pulsed current

30 waveform having current pulses with a magnitude of 0.2 mA, a pulse width

31 of 10 msec, and a frequency of 10 Hz will deliver roughly half as much drug

1   as the same device run at a frequency of 20 Hz. Given a constant drug

2   delivery area, e.g., of an electrode assembly, the applied current densities of

3   these two devices is the same and is above the high efficiency critical level I_c

4   so that both devices deliver drug transdermally by electrotransport with

5   higher efficiency and lower variability compared to devices which apply

6   electrotransport current at current densities below the critical level I_c. From

7   these two examples of the invention, one skilled in this art will appreciate

8   that a combination of frequency and duty cycle may be used to alter the rate

9   of drug delivery while maintaining the maximum applied current density, I_{max},

10   above I_c. FIG. 4 shows the waveforms for a device operated to have a

11   constant 9 msec pulse width, the frequency for a device operated according

12   to the lower waveform being one-half that of a device operated according to

13   the upper waveform (i.e., 50 Hz versus 100 Hz).

14   As is noted above, agent delivery efficiency is increased by exposure

15   of the site to a current density at or above I_c and for a time period equal to

16   or greater than a critical time, t_c. Generally speaking, for a pulsing

17   electrotransport device, the pulse width must equal or exceed t_c. Thus, t_c, in

18   a practice of this invention using pulsed current electrotransport devices and

19   for delivery of fentanyl, falls between about 0.5 msec and 30 msec. It is

20   believed that the minimum pulse width to cause transformation to the higher

21   efficiency state is about 10 msec for fentanyl.

22   Table 1 shows data which support the above observation. Table 1

23   shows drug delivery efficiency data for a device programmed to run at

24   frequencies of 1 Hz, 10 Hz and 625 Hz. A 31% duty cycle was employed.

25

26

TABLE 1

Frequency Hz	Pulse Width	Rate of Fentanyl Delivery µg/hr.	
		Without Bolus Treatment	After Bolus Treatment*
625	0.5 msec	7	34
10	31 msec	52**	52**
1	310 msec	48**	48**

* "Bolus Treatment" means a direct current bolus delivery of fentanyl for a period of 30 minutes at a current density of $0.1mA/cm^2$.

** The numbers in these two columns are the same because even at a pulse width as short as 31 msec, the skin site had already transformed to its highly efficient state.

Table 1 also indicates that fentanyl delivery is significantly lower at a high pulsing frequency of 625 Hz compared to the lower pulsing frequencies of 1 and 10 Hz. This phenomenon is called capacitive loss, which loss becomes greater as pulsing frequency is increased at a given duty cycle. Capacitive loss results because a portion of each pulse is consumed by the process of charging the skin without delivering drug. The shorter the pulse width (and hence the higher the pulsing frequency), the greater (relatively speaking) the capacitive loss for each pulse. Table 1 also shows that until a critical pulse width is achieved, regardless of frequency, no transformation of the body site agent delivery efficiency occurs.

Pulsed current electrotransport devices are well known in the art. Such devices are described in numerous technical articles and the patent literature including Bagniefski et al. "A Comparison of Pulsed and Continuous Current Iontophoresis", Journal of Controlled Release, 113-122, (1090); McNichols et al., U.S. patent 5,047,007; Sibalis U.S. Patent 5,135,478; R. Burnette et al. "Influence of Constant Current Iontophoresis on the Impedance and Passive Na^+ Permeability of Excised Nude Mouse Skin",

1   77 <u>J.Pharmaceutical Sciences</u> 492 (1988); Pikal et al, "Study of the

2   Mechanisms of Flux Enhancement Through Hairless Mouse Skin by Pulsed

3   DC Iontophoresis," 8 <u>Pharmaceutical Research</u> 365 (1991).

4   Another method of transdermally delivering a therapeutic agent (e.g.,

5   a drug) by electrotransport at an applied current density at or above the

6   critical level I_c but at a lower dosing/delivery rate (i.e., a rate which requires a

7   current lower than that achieved when applying a current sufficient to

8   achieve a current density of at least I_c) involves the intentional introduction of

9   competitive ions having the same (i.e., same polarity) charge as the

10   therapeutic agent ions. This approach, under the specific conditions

11   described, permits drug dosage control as well as providing enhanced

12   stability and enhanced efficiency of electrotransport of therapeutic agent.

13   This approach is generally discouraged in the patent literature because it

14   otherwise tends to reduce drug delivery efficiency. This aspect of this

15   invention is particularly applicable to electrotransport delivery of those drugs

16   or therapeutic agents which are therapeutically effective when (i) delivered at

17   low transdermal fluxes and/or (ii) when present in low concentrations in the

18   blood. Generally speaking, this aspect of the present invention is particularly

19   applicable to the electrotransport delivery of highly potent drugs or other

20   therapeutic agents.

21   The competitive ionic species can be loaded into the donor reservoir

22   (e.g., a biocompatible salt is added to the donor reservoir) before

23   electrotransport agent delivery and/or can be generated in situ during the

24   operation of the electrotransport device. Generation of competitive ionic

25   species in situ may be accomplished using a secondary electrode and

26   appropriate electrical control circuitry as described in Phipps et al US Patent

27   5,443,442 for example.

28   The amount of the competitive species intentionally added to the

29   donor reservoir will be specific to the drug or agents to be delivered and the

30   relative electrophoretic mobilities of the drug ions and the competing ionic

31   species. Generally, the competitive species will be ionic and should have

delivery characteristics similar to those of the drug being delivered. The quantity of co-delivered species to be added is selected so that the total current density is raised above the critical current density, I_c, where the ionic species efficiency is normalized or stabilized so that variation of delivery efficiency is no longer experienced.

The teachings in Theeuwes et al. U.S. Patent 5,080,646 may be utilized in determining the proper amount of competitive co-ion species to be added to the donor reservoir of an electrotransport delivery device. The patent discusses the processes involved in the transport of species through a biological surface such as skin, mucosa, or tissue. The Theeuwes et al patent provides a mathematical analysis which permits one skilled in this art, when unacceptable random variability of electrically-assisted drug flux is experienced, to select a suitable quantity and species of competetive co-ion to be delivered along with the drug or agent.

The transdermal electrotransport drug delivery efficiency may be increased, when using a pulsing electrotransport current, by maintaining the pulse width equal to or greater than t_c. In general, this requires the pulsing frequency to be maintained below about 100 Hz, and preferably less than about 10 Hz. The term "pulsing electrotransport current" as used herein means a current which varies in a periodic fashion. A pulsing electrotransport current which transforms the skin to the high efficiency transfer state is one where at least a portion of the periodic current waveform provides a current density below I_c, and another portion which has a sufficient magnitude and pulse width to effect transformation of the skin to the higher efficiency drug delivery state. This then provides the second of the two necessary and sufficient parameters (after current density I_c) which must be satisfied to apply this invention. As was noted above, pulsing frequencies in the relatively low ranges discussed here combined with sufficient duty cycle, provide the pulse width needed for in vivo skin drug delivery efficiency to increase. For example, a frequency of about 10 Hz (i.e., a period of about 100 msec) and a duty cycle of 31% was found to

1 provide a pulse width of 31 msec which was long enough to induce a skin

2 efficiency increase to deliver fentanyl at a current density of 0.1 mA/cm^2.

3   Reference is now made to FIG. 3 which depicts an exemplary

4 electrotransport device which can be used in accordance with the present

5 invention. FIG. 3 shows a perspective exploded view of an electrotransport

6 device 10 having an activation switch in the form of a push button switch 12

7 and a display in the form of a light emitting diode (LED) 14. Device 10

8 comprises an upper housing 16, a circuit board assembly 18, a lower

9 housing 20, anode electrode 22, cathode electrode 24, anode reservoir 26,

10 cathode reservoir 28 and skin-compatible adhesive 30. Upper housing 16

11 has lateral wings 15 which assist in holding device 10 on a patient's skin.

12 Upper housing 16 is preferably composed of an injection moldable elastomer

13 (e.g., ethylene vinyl acetate). Printed circuit board assembly 18 comprises

14 an integrated circuit 19 coupled to discrete electrical components 40 and

15 battery 32. Circuit board assembly 18 is attached to housing 16 by posts

16 (not shown in FIG. 3) passing through openings 13a and 13b, the ends of

17 the posts being heated/melted in order to heat stake the circuit board

18 assembly 18 to the housing 16. Lower housing 20 is attached to the upper

19 housing 16 by means of adhesive 30, the upper surface 34 of adhesive 30

20 being adhered to both lower housing 20 and upper housing 16 including the

21 bottom surfaces of wings 15.

22   Shown (partially) on the underside of circuit board assembly 18 is a

23 battery 32, which is preferably a button cell battery and most preferably a

24 lithium cell. Other types of batteries, such as sizes AAA and AAAA, may

25 also be employed to power device 10.

26   The circuit outputs (not shown in FIG. 3) of the circuit board assembly

27 18 make electrical contact with the electrodes 24 and 22 through openings

28 23,23' in the depressions 25,25' formed in lower housing, by means of

29 electrically conductive adhesive strips 42,42'. Electrodes 22 and 24, in turn,

30 are in direct mechanical and electrical contact with the top sides 44',44 of

31 drug reservoirs 26 and 28. The bottom sides 46',46 of drug reservoirs 26,28

1   contact the patient's skin through the openings 29',29 in adhesive 30. Upon

2   depression of push button switch 12, the electronic circuitry on circuit board

3   assembly 18 delivers a predetermined DC current to the

4   electrodes/reservoirs 22,26 and 24,28 for a delivery interval of predetermined

5   length, e.g., about 10 minutes. Preferably, the device transmits to the user a

6   visual and/or audible confirmation of the onset of the drug delivery, or bolus,

7   interval by means of LED 14 becoming lit and/or an audible sound signal

8   from, e.g., a "beeper". Drug (e.g., an analgesic drug such as fentanyl) is

9   then delivered through the patient's skin, e.g., on the arm, for the

10 predetermined (e.g., 10 minute) delivery interval. In practice, a user receives

11 feedback as to the onset of the drug delivery interval by visual (LED 14

12 becomes lit) and/or audible signals (a beep from the "beeper"). A preferred

13 device is described in commonly owned, pending patent application entitled

14 "Display for an Electrotransport Device", US Patent Application Serial

15 Number 08/410,112, filed March 24, 1995.

16   Anodic electrode 22 is preferably comprised of silver and cathodic

17 electrode 24 is preferably comprised of silver chloride.   Both reservoirs 26

18 and 28 are preferably comprised of polymer hydrogel materials as described

19 herein. Electrodes 22, 24 and reservoirs 26, 28 are retained by lower

20 housing 20. When the drug being delivered by electrotransport is cationic,

21 the anodic reservoir 26 is the "donor" reservoir which contains the drug and

22 the cathodic reservoir 28 contains a biocompatible electrolyte. When the

23 drug being delivered by electrotransport is anionic, the cathodic reservoir 28

24 is the "donor" reservoir which contains the drug and the anodic reservoir 26

25 contains a biocompatible electrolyte.

26   The push button switch 12, the electronic circuitry on circuit board

27 assembly 18 and the battery 32 are adhesively "sealed" between upper

28 housing 16 and lower housing 20. Upper housing 16 is preferably

29 composed of rubber or other elastomeric material. Lower housing 20 is

30 preferably composed of a plastic or elastomeric sheet material (e.g.,

31 polyethylene) which can be easily molded to form depressions 25,25' and cut

1 to form openings 23,23'. The assembled device 10 is preferably water

2 resistant (i.e., splash proof) and is most preferably waterproof. The system

3 has a low profile that easily conforms to the body thereby allowing freedom

4 of movement at, and around, the wearing site. The anode/drug reservoir 26

5 and the cathode/salt reservoir 28 are located on the skin-contacting side of

6 device 10 and are sufficiently separated to prevent accidental electrical

7 shorting during normal handling and use.

8   The device 10 adheres to the patient's body surface (e.g., skin) by

9 means of a peripheral adhesive 30 which has upper side 34 and body-

10 contacting side 36. The adhesive side 36 has adhesive properties which

11 assures that the device 10 remains in place on the body during normal user

12 activity, and yet permits reasonable removal after the predetermined (e.g.,

13 24-hour) wear period. Upper adhesive side 34 adheres to lower housing 20

14 and retains the electrodes and drug reservoirs within housing depressions

15 25,25' as well as retains lower housing 20 attached to upper housing 16.

16   The push button switch 12 is located on the top side of device 10 and

17 is easily actuated through clothing. A double press of the push button

18 switch 12 within a short period of time, e.g., three seconds, is preferably

19 used to activate the device 10 for delivery of drug, thereby minimizing the

20 likelihood of inadvertent actuation of the device 10.

21   Upon switch activation an audible alarm signals the start of drug

22 delivery, at which time the circuit supplies a predetermined level of DC

23 current to the electrodes/reservoirs for a predetermined (e.g., 10 minute)

24 delivery interval. The LED 14 remains "on" throughout the delivery interval

25 indicating that the device 10 is in an active drug delivery mode. The battery

26 preferably has sufficient capacity to continuously power the device 10 at the

27 predetermined level of DC current for the entire (e.g., 24 hour) wearing

28 period.

29   The present invention is particularly useful in the transformation of

30 human skin in the transdermal electrotransport delivery of drugs to humans.

1   However, the invention also has utility in delivering drugs to other animals

2   and is not limited to humans.

3   The terms "agent" and "drug" are used interchangeably herein and

4   are intended to have their broadest interpretation as any therapeutically

5   active substance which is delivered to a living organism to produce a

6   desired, usually beneficial, effect. In general, this includes therapeutic

7   agents in all of the major therapeutic areas including, but not limited to, anti-

8   infectives such as antibiotics and antiviral agents, analgesics and analgesic

9   combinations, anesthetics, anorexics, antiarthritics, antiasthmatic agents,

10   anticonvulsants, anti-depressants, antidiabetic agents, antidiarrheals,

11   antihistamines, anti-inflammatory agents, antimigraine preparations,

12   antimotion sickness preparations, antinauseants, antineoplastics,

13   antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics,

14   antispasmodics including gastrointestinal and urinary antispasmodics,

15   anticholinergics, sympathomimetrics, xanthine derivatives, cardiovascular

16   preparations including calcium channel blockers, beta-blockers,

17   antiarrythmics, antihypertensives, diuretics, vasodilators including general,

18   coronary, peripheral and cerebral vasodilators, central nervous system

19   stimulants, cough and cold preparations, decongestants, diagnostics,

20   hormones, hypnotics, immunosuppressives, muscle relaxants,

21   parasympatholytics, parasympathomimetrics, proteins, peptides, polypeptides

22   and other macromolecules, psychostimulants, sedatives and tranquilizers.

23   The present invention can be used to deliver transdermally by

24   electrotransport the following drugs: interferons, alfentanyl, amphotericin B,

25   angiopeptin, baclofen, beclomethasone, betamethasone, bisphosphonates,

26   bromocriptine, buserelin, buspirone, calcitonin, ciclopirox, olamine, copper,

27   cromolyn sodium, desmopressin, diclofenac diflorasone, diltiazem,

28   dobutamine, dopamine agonists, dopamine agonists, doxazosin, droperidol,

29   enalapril, enalaprilat, fentanyl, encainide, G-CSF, GM-CSF, M-CSF, GHRF,

30   GHRH, gonadorelin, goserelin, granisetron, haloperidol, hydrocortisone,

31   indomethacin, insulin, insulinotropin, interleukins, isosorbide dinitrate,

24

1   ketoprofen, ketorolac, leuprolide, LHRH, lidocaine, lisinopril, LMW heparin,

2   melatonin, methotrexate, metoclopramide, miconazole, midazolam, nafarelin,

3   nicardipine, NMDA antagonists, octreotide, ondansetron, oxybutynin, PGE_1,

4   piroxicam, pramipexole, prazosin, prednisolone, prostaglandins, scopolamine,

5   seglitide, sufentanil, terbutaline, testosterone, tetracaine, tropisetron,

6   vapreotide, vasopressin, verapamil, warfarin, zacopride, zinc, and zotasetron.

7   This invention is also believed to be useful in the transdermal

8   electrotransport delivery of peptides, polypeptides and other macromolecules

9   typically having a molecular weight of at least about 300 daltons, and

10   typically a molecular weight in the range of about 300 to 40,000 daltons.

11   Specific examples of peptides and proteins in this size range include, without

12   limitation, LHRH, LHRH analogs such as buserelin, gonadorelin, nafarelin

13   and leuprolide, GHRH, insulin, heparin, calcitonin, endorphin, TRH, NT-36

14   (chemical name: N=[[(s)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-

15   prolinamide), liprecin, pituitary hormones (e.g., HGH, HMG, HCG,

16   desmopressin acetate, etc,), follicle luteoids, αANF, growth hormone

17   releasing factor (GHRF), βMSH, TGF-β, somatostatin, atrial natriuretic

18   peptide, bradykinin, somatotropin, platelet-derived growth factor,

19   asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic

20   gonadotropin, corticotropin (ACTH), epidermal growth factor, erythropoietin,

21   epoprostenol (platelet aggregation inhibitor), follicle stimulating hormone,

22   glucagon, hirulogs, hyaluronidase, interferons, insulin-like growth factors,

23   interleukins, menotropins (urofollitropin (FSH) and LH), oxytocin,

24   streptokinase, tissue plasminogen activator, urokinase, vasopressin, ACTH

25   analogs, ANP, ANP clearance inhibitors, angiotensin II antagonists,

26   antidiuretic hormone agonists, antidiuretic hormone antagonists, bradykinin

27   antagonists, CD4, ceredase, CSF's, enkephalins, FAB fragments, IgE

28   peptide suppressors, IGF-1, neuropeptide Y, neurotrophic factors, opiate

29   peptides, parathyroid hormone and agonists, parathyroid hormone

30   antagonists, prostaglandin antagonists, pentigetide, protein C, protein S,

1   ramoplanin, renin inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines,

2   vasopressin antagonist analogs, alpha-1 anti-trypsin (recombinant).

3   Generally speaking, it is most preferable to use a water soluble form

4   of the drug or agent to be delivered. Drug or agent precursors, i.e., species

5   which generate the selected species by physical or chemical processes such

6   as ionization, dissociation, dissolution or covalent chemical modification (i.e.,

7   prodrugs), are within the definition of "agent" or "drug" herein. "Drug" or

8   "agent" is to be understood to include charged and uncharged species as

9   described above.

10   While the disclosure has focussed upon the electrotransport delivery

11   of ionic species, the present invention is also applicable to the

12   electrotransport delivery of uncharged species, e.g., by electroosmosis.

13   Thus, the transformation of the skin into the high efficiency transport state is

14   not limited to electrically assisted transport of ionic species but also to

15   electroosmotic delivery of uncharged (i.e., non-ionized) species.

16   The following examples illustrate some of the advantages of the

17   present invention.

18

19   <u>EXAMPLE 1</u>

20   Current Density and Increased Efficiency

21   This study evaluated the effect of applied current on electrotransport

22   drug delivery efficiency. Drug delivery efficiency is expressed in terms of the

23   rate of drug delivery per unit of applied current. The study involved the

24   application of electrotransport devices to eighteen healthy male volunteers

25   for a duration of about one day.

26   The two electrotransport treatments involved the delivery of fentanyl

27   from a donor reservoir containing an aqueous solution of fentanyl HCl and

28   having a skin contact area of 5 cm^2, at a baseline current of 100 μA. Thus,

29   the applied electrotransport current density was 20 μA/cm^2 (= 100 μA ÷ 5

30   cm^2). Six of the eighteen volunteers were administered 4 bolus doses during

31   the first hour of treatment by applying current levels of 1300 μA (i.e., an

1   applied electrotransport current density of 260 μA/cm^2) for a duration of 2.5

2   minutes at 15 minute intervals. Following the administration of the four

3   boluses in the first hour of treatment, these six volunteers received

4   continuous transdermal electrotransport fentanyl administration at a current

5   density of 20 μA/cm^2 from hour 2 through 24 hours. The remaining twelve

6   volunteers received continuous transdermal electrotransport fentanyl

7   administration at a current density of 20 μA/cm^2 over the entire 24 hour

8   delivery period. After the treatment period, the electrotransport devices were

9   removed. The skin site was then washed to remove any residual fentanyl.

10   Blood samples were taken over the entire 24 hour period commencing

11   with the application of current from the electrotransport devices. Serum

12   fentanyl concentrations were used to calculate mean transdermal fentanyl

13   fluxes using subject specific pharmacokinetic parameters and conventional

14   methods.

15   FIG. 5 shows that once a skin site receives a minimum level of

16   current (for a fixed electrode area) for a sufficient duration, a high

17   electrotransport efficiency state is achieved. FIG. 5 shows the mean serum

18   fentanyl concentration in the blood of the subjects over the 24 hour testing

19   period. As is shown in the uppermost curve (◊ ••• ◊ ••• ◊) in FIG. 5, the six

20   volunteers which received the four 260 μA/cm^2, 2.5 minute bolus

21   administrations in the first hour exhibited higher efficiency fentanyl

22   transdermal delivery than the group of twelve subjects shown as three

23   groups of four in the three lower curves (to emphasize inherent variability)

24   who received only the 20 μA/cm^2 constant DC current. Once this high-

25   efficiency transport state is achieved, more drug is delivered through the skin

26   per unit of applied current. Further, the effect lasted the entire 24 hours of

27   the treatment. This is indicated by the vertical separation between the upper

28   curve and the three lower curves in FIG. 5.

29   Specifically, the six volunteers who received the four 260 μA/cm^2

30   doses in the first hour of treatment exhibited a mean transdermal fentanyl

31   flux of 113 μg/h while the twelve volunteers who received only the 20 μA/cm^2

1 baseline current exhibited a mean transdermal fentanyl flux of 57 µg/h. This

2 indicates that the efficiency was enhanced by about a factor of two as a

3 result of the initial high current density boluses.

4

5   EXAMPLE 2

6 Current Density and Fentanyl Flux

7   This study was undertaken to evaluate the relationship of current

8 density and drug flux in the transdermal electrotransport delivery of fentanyl.

9 Electrotransport devices, delivering constant DC currents, were applied to 8

10 healthy male volunteers for a duration of 24 hours. The three

11 electrotransport treatment regimens in this study differed only in the applied

12 electrotransport current (and therefore current density) levels. The

13 electrotransport devices delivered fentanyl through the skin from a donor

14 hydrogel having a skin contact surface area of 5 cm^2. The gels were

15 imbibed with an aqueous solution of fentanyl HCl. The current density levels

16 used in this study were 10, 20, and 40 µA/cm^2. After a 24 hour treatment

17 period, the electrotransport devices were removed. The skin site was then

18 washed to remove any residual fentanyl. All 8 volunteers received each

19 treatment approximately 1 week apart.

20   For each treatment, blood samples were taken over a 24 hour period

21 commencing with the application of current from the electrotransport devices.

22 Serum fentanyl concentrations over the first 24 hours are shown in FIG. 6.

23 The top curve (– ▲ – ▲ – ▲ –) in FIG. 6 was the 200 µA treatment (i.e., 40

24 µA/cm^2), the middle curve (-□ -□ -□ -) the 100 µA treatment (i.e., 20 µA/cm^2)

25 and the bottom curve (–0–0–0–) the 50 µA treatment (i.e., 10 µA/cm^2). As

26 in Example 1, the serum fentanyl concentrations from each patient were

27 used to calculate mean drug rate and the mean total amount of drug

28 delivered. A drug delivery efficiency level for each treatment was derived by

29 dividing the mean fentanyl rate by the current density applied to the skin.

30   The average transdermal fentanyl rates were 19, 73 and 173 µg/h at

31 the applied current densities 10, 20 and 40 µA/cm^2, respectively. This data

1 shows a non-linear relationship between applied current and transdermal

2 electrotransport drug flux within the electrotransport current density range of

3 10 to 40 $\mu A/cm^2$. An almost ten-fold increase in drug rate was observed as

4 the current was increased four-fold from 50μA to 200 μA. This unexpected

5 result indicates that the efficiency of fentanyl delivery was enhanced by a

6 factor of about 2.5-fold due to the change in current density from 10 to 40

7 $\mu A/cm^2$.

8

9 <u>EXAMPLE 3</u>

10 This study was undertaken to evaluate the relationship between

11 current density and drug flux in the transdermal electrotransport delivery of

12 goserelin. The study involved the application of electrotransport devices,

13 applying constant current, to 12 normal male volunteers for a duration of 8

14 hours.

15 The two electrotransport treatment regimens in this study differed only

16 in applied current density levels. The electrotransport devices delivered

17 goserelin through the skin from polyvinyl alcohol (PVOH)-based donor

18 hydrogels having a skin-contact surface area of 4 cm^2. The gels contained

19 an aqueous goserelin solution. The current density levels used in this study

20 were 50 and 100 $\mu A/cm^2$. After an 8 hour treatment period, the

21 electrotransport devices were removed. The skin site was then washed to

22 remove any residual goserelin. All 12 volunteers received each treatment

23 seven days apart.

24 For each treatment, seven blood samples were taken over a 24 hour

25 period commencing with the application of current from the electrotransport

26 devices. Serum goserelin concentrations from each patient were used to

27 calculate mean drug flux and the mean total amount of drug delivered.

28 FIG. 8 shows the goserelin blood plasma concentrations for the 8

29 hour duration of electrotransport administration for the two current densities

30 (i.e., 50 and 100 $\mu A/cm^2$). The 100 $\mu A/cm^2$ curve is the upper curve in FIG.

31 8 while the lower curve in FIG. 8 is the 50 $\mu A/cm^2$ data. From this

1 concentration data, transdermal goserelin fluxes were calculated. The

2 average transdermal goserelin flux was 5.8 μg/h at an applied current

3 density of 50 μA/cm^2 while the average transdermal flux of goserelin was

4 21.6 μg/h at an applied current density of 100 μA/cm^2. Thus, a non-linear

5 relationship between applied current density and drug flux was shown by the

6 data. An almost four-fold increase in drug flux is observed as the current

7 density rises from 50 to 100 μA/cm^2. This data also suggests the existence

8 of a critical current density, I_c, which for transdermal electrotransport delivery

9 of goserelin falls between 50 and 100 μA/cm^2, above which more drug is

10 delivered through the skin per unit of applied current.

11 The remaining example utilizes a pulsing electrotransport

12 current, and is therefore relevant only to a preferred aspect of the present

13 invention wherein the applied electrotransport current is a pulsing current

14 with current pulses having a pulse width of at least 5 msec, and more

15 preferably a pulse width of at least 10 msec.

16

17 <u>EXAMPLE 4</u>

18 Pulsing Frequency and Fentanyl Flux

19 This study assessed the effect of pulsing frequency on the

20 electrotransport delivery of fentanyl using pulsed current waveforms. The

21 frequencies evaluated in this study were 1, 10, and 625 Hz.

22 The electrotransport devices were configured to deliver a 200 μA

23 square wave current pulse, having a 31% duty cycle. The electrotransport

24 devices delivered fentanyl through the skin from a donor hydrogel having a

25 skin contact surface area of 2 cm^2. Thus, during the applied electrotransport

26 current pulses, the current density was 100 μA/cm^2 (= 200 μA ÷ 2 cm^2). The

27 gels were imbibed with an aqueous solution of fentanyl HCl. After treatment

28 periods of varying duration, the electrotransport devices were removed. The

29 skin site was then washed to remove any residual fentanyl.

1   For each treatment, blood samples were taken commencing with the

2   application of current from the electrotransport devices. Serum fentanyl

3   levels from each patient were used to calculate mean drug flux.

4   FIG. 7 shows that the use of a square-wave frequency of 625 Hz

5   resulted in minimal fentanyl flux. This is shown in the lower most nearly

6   horizontal curve in FIG. 7. The use of the lower pulsing frequencies, 1 and

7   10 Hz, resulted in increased fentanyl flux. This is shown in the upper two

8   curves of FIG. 7. No statistically significant difference in fentanyl flux was

9   observed between 1 and 10 Hz. These results suggest that the use of lower

10 pulsing frequencies results in higher electrotransport delivery efficiency of

11 fentanyl.

12   The above disclosure will suggest many alternatives, permutations,

13 and variations of the invention to one skilled in this art without departing from

14 the scope of the invention. The above disclosure is intended to be

15 illustrative and not exhaustive. All such, permutations, variations, and

16 alternatives suggested by the above disclosure are to be included within the

17 scope of the attached claims.